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Interference No. 105,358
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Michael P. Tierney)

POLICE S. **REDDY**, SURESH K. TIKOO, and
LORNE A. BABIUK,
(U.S. Patent 6,492,343)
Junior Party,

v.

MICHAEL A. **JOHNSON**, JEFFREY M. HAMMOND,
RICHARD J. McCOY and MICHAEL G. SHEPPARD
(U.S. Application 09/485,512)
Senior Party.

Patent Interference No. **105,358**
(Technology Center 1600)

REDDY SUBSTANTIVE MOTION 3
(for Judgment Pursuant to 37 C.F.R. § 41.121(a)(I)(iii) on the ground of Indefiniteness under 35 U.S.C. § 112, second paragraph)

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REDDY SUBSTANTIVE MOTION 3
(for Judgment Pursuant to 37 C.F.R. § 41.121(a)(I)(iii) on the ground of Indefiniteness under 35 U.S.C. § 112, second paragraph).

I. REQUEST FOR RELIEF

Junior party REDDY, *et al.* ("Reddy") moves under 37 C.F.R. § 41.121(a)(I)(iii) for judgment against Senior Party JOHNSON, *et al.* ("Johnson") on all of Johnson's claims in interference because they do not distinctly claim the subject matter of the invention as required under Paragraph 2 of 35 U.S.C. § 112.

II. REASONS FOR RELIEF REQUESTED

A. Background

The technology at issue in this interference relates to recombinant viruses that are engineered to be useful as vaccines. The particular viruses involved are porcine adenoviruses. An adenovirus is a DNA virus that infects the respiratory tract, intestines, and other mucous membranes. Fact ¶ 29.

For nearly 20 years, scientists have recognized adenoviruses as having the potential to be recombined with foreign genes encoding antigens of more virulent pathogens for the purpose of creating vaccines. Fact ¶¶ 30, 31. Since 1987, researchers have studied the potential use of adenoviruses as vectors for the delivery and expression of foreign DNA. Fact ¶ 30. One of the challenges that such scientists face is to insert the foreign genes (or "heterologous DNA") in such a way that the adenovirus retains the ability to replicate. Fact ¶ 48. If the foreign genes are inserted into a location that codes for polypeptides that are essential to viral replication, then the resulting adenovirus is "replication-defective." Fact ¶ 49. Replication-defective adenoviruses cannot be grown except in a complementing "helper" cell-line that can produce the essential products of

the deleted region or regions of the adenovirus. Fact ¶¶ 50-51. In the absence of a complementing cell-line, viral DNA that has been recombined to eliminate or disable one or more essential genes will not express a virus. Fact ¶ 50. Such recombinants are therefore known as "helper-dependent" recombinants. Fact ¶ 52.

By experimentation it is sometimes possible to identify certain areas of the adenovirus genome that are not essential for viral replication. Fact ¶ 53. In order to understand which regions of a given adenovirus are needed for replication, it is important to understand the life cycle of the adenovirus. Transcription of adenovirus DNA is accomplished in two phases: the early phase and the late phase. Fact ¶ 35. During the early phase, the virus selectively transcribes certain "early genes" that perform a variety of functions to create the necessary pre-conditions for viral replication. Fact ¶ 36. The adenovirus early genes are identified by number E1 through E4. Fact ¶ 37.

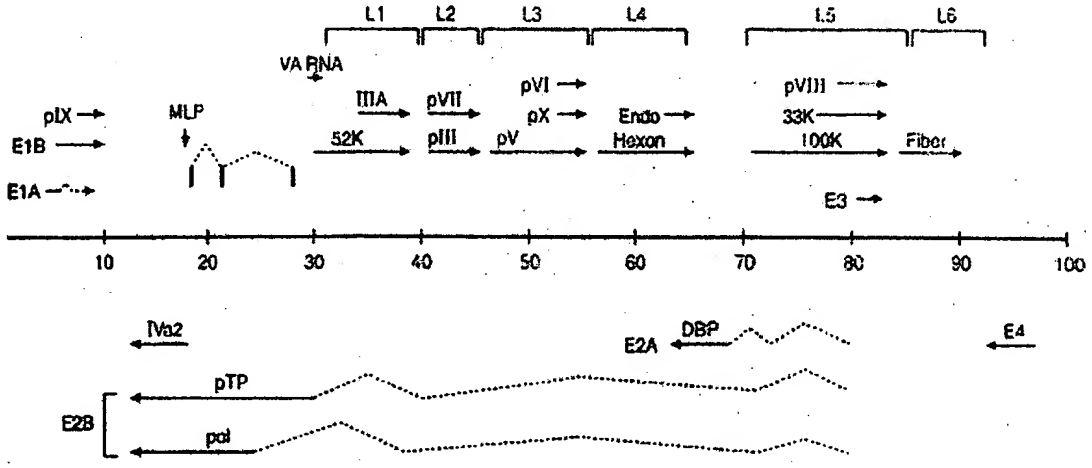
Once early-phase transcription is complete, transcription of the "late genes" may begin. Fact ¶ 38. The products of late genes include capsid proteins which are critical structural elements required for the virus to survive. Fact ¶¶ 32, 39. By convention, adenovirus proteins are identified by Roman numerals, however the major capsid proteins are also known by other names such as "fiber" for pIV, "hexon" for pII, and "penton" for pIII. Fact ¶¶ 33, 34. Structural proteins, such as the pVIII protein, are products of late-phase transcription. Fact ¶ 45. Some early genes also encode polypeptides that are essential for viral replication. Fact ¶ 46. For instance, in human adenoviruses, E1 is essential for replication. Fact ¶ 52. Other early regions may be dispensable when the virus is to be grown in a cell culture in a laboratory. Fact ¶ 47.

Viral DNA is transcribed in blocks known as transcription units, which can be processed into multiple mRNAs. Fact ¶ 40. A single mRNA may consist of one or more "open reading frames," each of which can be translated into a protein. Fact ¶ 41. The open reading frame for one gene or protein may overlap with the open reading frame for another. Fact ¶ 42. As a result, the same sequence of nucleotides may form part of more than one gene and thus, more than one gene may be affected when a given sequence of nucleotides is deleted or recombined. Fact ¶ 43. The arrangement of genes or "open reading frames" on a viral genome is commonly illustrated in a "genome map."

Adenoviruses have an upper limit to the amount of genetic information they can hold. Fact ¶ 55. For this reason, scientists working with recombinant adenoviruses are concerned with identifying ways to delete native DNA sequences in order to make room for foreign DNA sequences of interest. Fact ¶ 56. One way that this is accomplished is by identifying genes that encode for products that are non-essential in viral replication Fact ¶¶ 53, 54. As is discussed below, this is the approach that Johnson used.

More difficult, but potentially more advantageous, is the approach of developing complementary cell lines that are customized to provide the elements that the virus needs to replicate. When such "helper" cell lines are available, the genes associated with the elements that the helper can produce are rendered superfluous for replication, and may be deleted to make room for foreign genes of interest. Fact ¶¶ 50, 51. If helper cell lines are available, it is possible to delete genes that are needed to make the virus replication-competent. Fact ¶¶ 56, 58. Deletions of native adenovirus DNA may prevent the expression of any genes that are associated with the deleted nucleotides. Fact ¶ 57.

All of Johnson's claims in interference contain limitations directed to insertion of heterologous DNA within certain map unit ranges of PAV3. Fact ¶ 1. A genome is "mapped" by dividing the whole genome into 100 units. Fact ¶ 4. In 1998 Reddy published a "genome map" of PAV3 that lays out the elements of PAV3 on such a scale, which is reproduced below. Fact ¶ 27. (Ex. 2029, Reddy (1998), at page 416, Figure 1).



The arrows represent genes or groups of genes that are transcribed in PAV3. Fact ¶ 27. The bodies of the arrows show where the transcribed nucleotides are located, and the arrow heads identify the termination point of the genes. Fact ¶ 27. As shown above, the E3 region begins after map unit 80. The illustration above shows, for example, that nucleotides encoding the E3 genes also encode the pVIII protein associated with late regions (specifically, the L5 region, in PAV3). Fact ¶ 28. The Reddy paper was published in 1998. Fact ¶ 27.

Because map units are defined in relation to the total size of the genome, the specific nucleotide to which a given map unit refers depends on the size of the genome.

Fact ¶ 5. For example, unit 81 refers to the 810th nucleotide in a genome of 1000 nucleotides (81*10 = 810), and to the 4,050th nucleotide in a genome of 5000 nucleotides (81*50 = 4,050). Fact ¶ 5.

B. The Disclosures of the '512 Application

The '512 Application (Ex. 2002) simultaneously discloses three *different* sizes for the PAV3 genome: 34.8 kb, 35kb and 34.094 kb. Fact ¶ 8. Johnson's Australian priority application describes the size of the PAV3 genome as being 34.8 kb (Ex. 2003). Fact ¶ 24. The reference to 35kb genome size for PAV3 appears for the first time in the original PCT patent application (Ex. 2004) at Figure 1. Fact ¶ 25. Johnson added the reference to 34.094 kb genome size for PAV3 when he added Figure 15 to his PCT application through an amendment submitted November 11, 1999, to the International Preliminary Examining Authority ("IPEA") (Ex. 2034).[1] Fact ¶ 26. The '512 Application nowhere defines which of these three sizes is to be used as the basis for the map unit ranges set

[1] This is a substantive amendment and is new matter. Accordingly, Johnson's amendment violates WIPO Patent Cooperation Treaty Rule 34(2)(b), which states, "The applicant shall have a right to amend the claims, the description, and the drawings, in the prescribed manner and within the prescribed time limit, before the international preliminary examination report is established. The amendment shall not go beyond the disclosure in the international application as filed." Since the genome size of 34.094 kb was not known in the art until Reddy's 1998 publication, this addition was clearly new matter.

forth in the claims. Fact ¶ 9. Current research demonstrates that the correct size of the PAV3 genome is 34.094 kb. Fact ¶ 11.

C. Legal Standard for Proving Indefiniteness

A claim is invalid as indefinite "[i]f the scope of the invention sought to be patented is unclear from the language of the claim[.]" *In re Wiggins*, 488 F.2d 538, 541, 179 U.S.P.Q. 421, 423 (CCPA 1973). Whether a claim is indefinite is a question of law. *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692, 57 U.S.P.Q.2d 1293, 1297 (Fed. Cir. 2001). It turns on whether "those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification." *Id.*; *Ex parte Tanksley*, 37 U.S.P.Q.2d 1382, 1387, *16 (BPAI 1994). The primary purpose of the definiteness requirement is to give to the public notice as to what constitutes infringement, so that one reading the patent knows "what may or may not be manufactured." *Norton Co. v. Bendix Corp.*, 449 F.2d 553, 557, 171 U.S.P.Q. 449, 451 (2nd Cir. 1971); *United Carbon Co. v. Binney Smith Co.*, 317 U.S. 228, 232, 236 (1942). Although the degree of precision necessary for definiteness "is a function of the nature of the subject matter[,]" *Mossman v. Broderbund Software, Inc.*, 51 U.S.P.Q.2d 1752, 1757 (E.D. Mich. 1999), "an invention must be capable of accurate definition, and it must be accurately defined, to be patentable." *United Carbon Co.*, 317 U.S. at 237. Finally, if the meaning of a claim is in doubt, especially if there is close prior art, the claim must be declared invalid. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218, 18 U.S.P.Q.2d 1016, 1031 (Fed. Cir. 1991).

D. Johnson's Claims in Interference are Indefinite

For the purposes of this motion, Johnson claim 1 is illustrative. Fact ¶ 2. It reads:

> A recombinant porcine adenovirus expressing heterologous DNA, said DNA of interest being stably integrated into a site of said recombinant porcine adenovirus genome wherein said site is selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3.

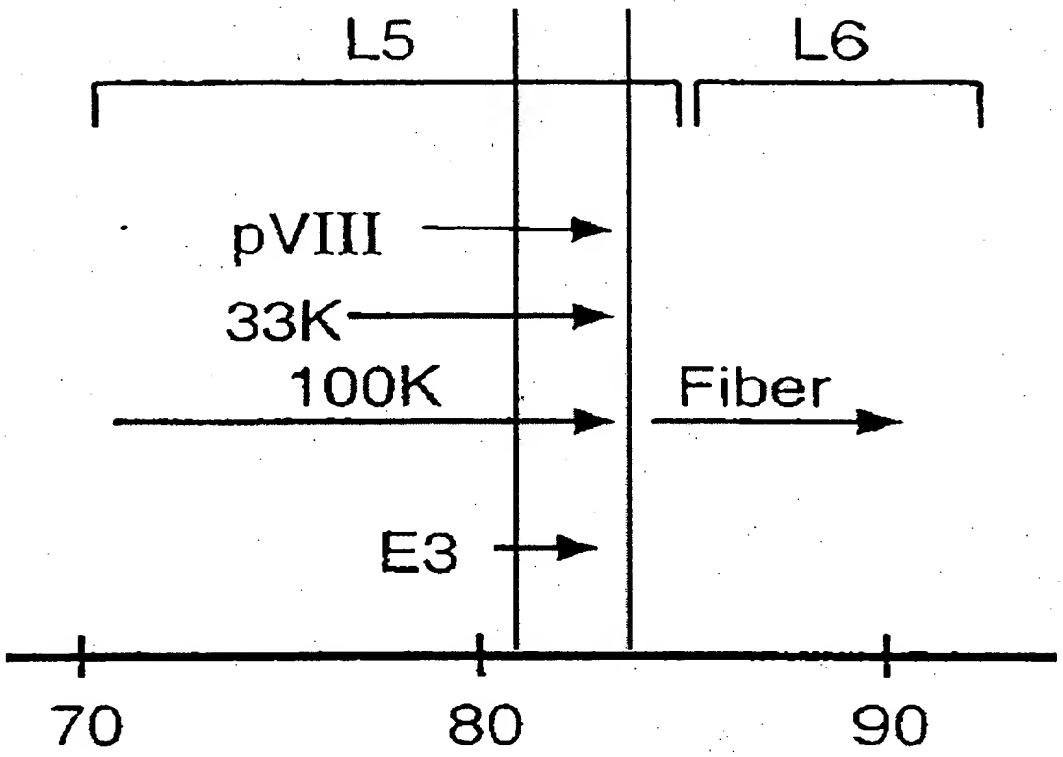
In sum, this claim is directed to a porcine adenovirus incorporating heterologous DNA in one or more of a Markush group of map unit limitations. Claim 1 is representative of all of Johnson's claims in interference because they all incorporate one or more map unit limitations. Fact ¶ 3. In order to understand the scope of these claims, a person of skill in the art would first try to determine how the specified map units correspond to the PAV3 genome. Fact ¶ 21. To do that, the first step would be to determine how many nucleotides correspond to a single map unit. Ordinarily, this is a matter of simple math:

Genome Size / 100 = Nucleotides per Map Unit

But in this instance, a person of skill in the art would by stymied from the outset because it would be impossible to determine which of the three genome sizes identified in the specification of the '512 application are intended to be used as the basis for the map units set out in Johnson's claims. Fact ¶ 9. Thus, the use of map units in the claims of the '512 application does not define nucleotide regions of the genome to a person of ordinary skill in the art. Fact ¶ 10.

Claim 30, which is directed to map units 81-84, illustrates the point. Using a map unit scale that is based on the correct size of PAV3 (34.094), map units 81-84 of PAV3 are shown in the following illustration that is based on an excerpt of Reddy's 1988 PAV3 genome map (Fact ¶ 11) (for illustration purposes only, and not drawn precisely to scale):

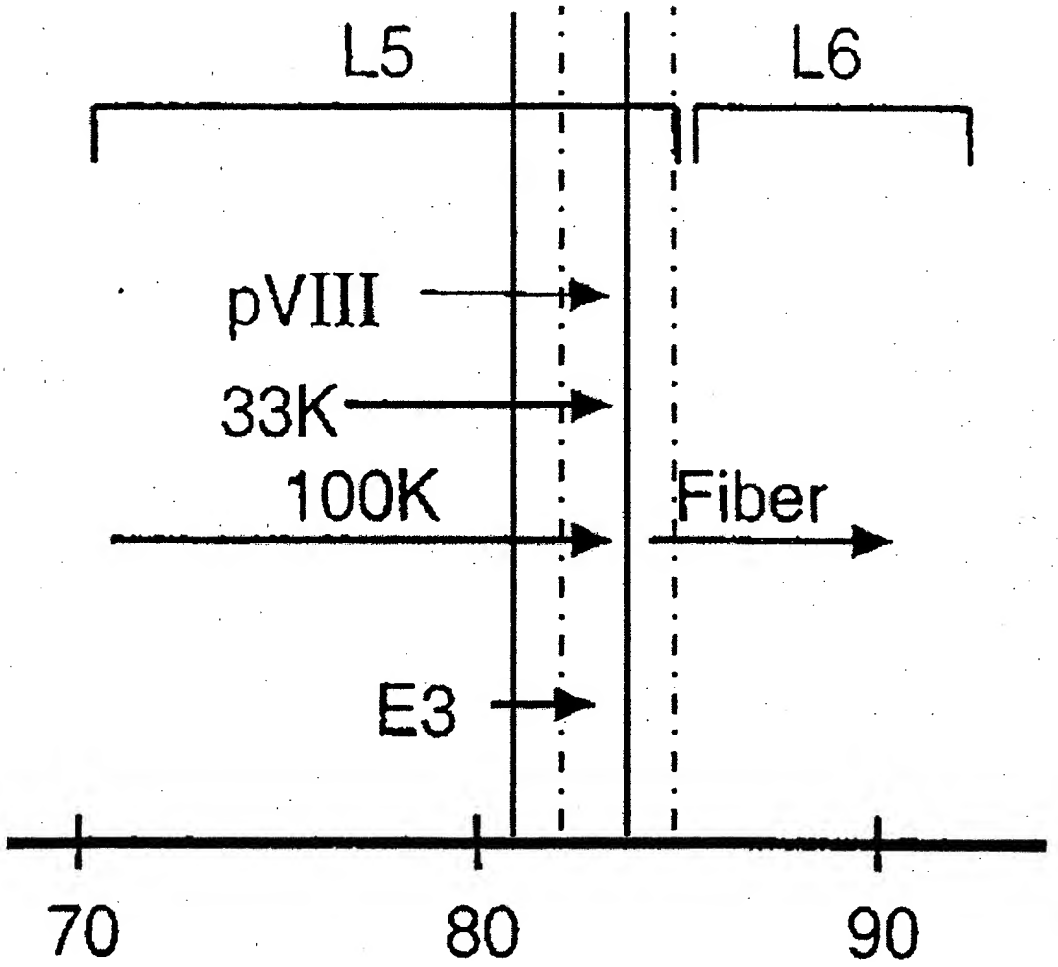
If



The scope of claim 30 might be defined to cover recombinant PAV3 incorporating heterologous DNA anywhere between the solid vertical lines superimposed above.

However, using the 34.8 kb genome size disclosed in the '512 application would yield a different result. Map units 81-84 would then refer to a scale of 348 nucleotides per unit. Fact ¶ 13. Accordingly, map unit 81 would correspond to nucleotide 28,188 (because 81*348=28,188). Fact ¶ 14. Map unit 84 would correspond to nucleotide 29,232 (because 84*348=29,232). Id. However, it is now known that the correct size of PAV3 is 34.094 kb, and each map on the scale above thus corresponds to 340.94 nucleotides. Fact ¶ 15. Accordingly, using the correct map-unit scale, nucleotide 28,188 would correspond to map unit 82.6 (because 28,188/340.94 = 82.6), and nucleotide 29,232 would correspond to map unit 85.73 (because 29,232/304.94 = 85.73). Fact ¶ 16.

The claimed range therefore shifts significantly (again provided for illustration purposes only):



In the diagram shown above, the broken vertical lines depict the nucleotides specified if the genome size is assumed to be 34.8kb. Notably, the range shifts so far as to encompass within it the fiber gene of L6 – a gene that is essential to viral replication.

Fact ¶ 18. The splice acceptor site of the fiber gene begins at nucleotide 28910. Fact ¶ 19.

Because the patent does not call out which of the three genome sizes should be employed when interpreting the map unit ranges of the claims, the scope of claim 30 is indefinite. Fact ¶9. For the same reasons, all of Johnson's other claims in interference are indefinite. All of them purport to be defined in terms of map units which are vague and not consistently defined in the '512 specification (Ex. 2002). Fact ¶¶ 2, 3, 9.

Johnson's claims 28 and 30 are made even *less* definite by Johnson's use of the term "about" to qualify his claims. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d at 1218, 18 U.S.P.Q.2d at 1030 (use of the phrase "at least about 160,000" was indefinite). The use of this phrase blurs the already uncertain lines of Johnson's claims. Taking again the example of claim 30, as shown above the range 81-84 might be read, in light of Johnson's self-contradictory disclosure, to refer to map units 82.6 to 85.73. Fact ¶ 16. If a single additional map unit is added to the range at each end through the use of the phrase "about," that would yield a spread of 80 to 86.73. That equates to a total range of 6.73 map units – more than double the 3 map unit range of the claim as it is written. Claim 28 presents an even stronger case of indefiniteness, since it purports to cover an even narrower range (97-99.5), that would be stretched to an even greater degree by the use of the phrase "about."

As demonstrated above, by broadening the scope of the claims through imprecision, Johnson expands their scope by more than 100% in some cases. This is a material difference in the context of this invention, especially in light of the narrowness of Johnson's enabling disclosure. At best, Johnson's disclosure enables one of skill in the

art to make insertions of foreign DNA at certain specific restriction sites disclosed in the examples of his specification. Fact ¶ 1.

Further, Johnson claims 26, 31 and 32 specify the additional limitation that the heterologous DNA be inserted into a "non-essential region" of the recombinant porcine adenovirus vector. Fact ¶ 59. These claims require that insertions be made in *non-essential* regions of the genome. Johnson does not enable or describe producing a replication-defective virus. Fact ¶ 23. By expanding the scope of his claims by imprecision, Johnson pushes them even further into regions of the genome that are clearly essential for viral replication, such as the Fiber gene. Fact ¶¶ 18-19. This is especially material in the case of claims 26, 31 and 32, where the scope of the invention sought to be patented is unclear from the language of the claim. For example, as shown in the above illustrations the range 81-84 either overlaps, or is tightly bounded by, essential regions of the genome. Fact ¶¶ 18, 28. Johnson should not be permitted to claim by imprecision that which he could not claim expressly.

III. CONCLUSION

Johnson's claims suffer from a fatal flaw: they all refer to "map unit" ranges that are ambiguous at best, given the specification's contradictory guidance as to the size of the PAV3 genome. Reddy respectfully requests that the Board grant this motion and find Johnson's claims indefinite.

Dated: February 24, 2006

Respectfully submitted,

By 

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APPENDIX A (EVIDENCE IN SUPPORT OF THE MOTION)

In support of this motion, Reddy relies on Reddy Exhibit Nos. 2002-2005, 2009, 2013, 2022, 2029, 2033, and 2034:

1. Johnson U.S. Patent Application No. 09/485,512, filed May 5, 2000 (Ex. 2002).
2. Johnson Australian Provisional Patent Application No. PO 8560, filed August 14, 1997 (Ex. 2003).
3. Johnson International Patent Application No. PCT/AU98/00648, filed August 14, 1998 (Ex. 2004).
4. Declaration of Interference – Bd. R. 203(d), Paper No. 1, mailed October 19, 2005 (Ex. 2005).
5. Declaration of Katherine R. Spindler, Ph.D. (Ex. 2009).
6. Johnson Clean Copy of Claims, 9 pages (Ex. 2013).
7. P. Seshidhar Reddy et al., *Sequence Analysis of Putative pVIII, E3 and Fibre Regions of Porcine Adenovirus Type 3,* VIRUS RESEARCH 36, 97-106. (1995) (Ex. 2022).
8. P. Seshidhar Reddy et al., *Nucleotide Sequence and Transcription Map Of Porcine Adenovirus Type 3,* VIROLOGY 251(2):414-426 (1998) (Ex. 2029).
9. Second Declaration of Dr. Jeffrey Michael Hammond Under 37 C.F.R. §1.132, 7 pages, with Response to Office Action mailed on February 27, 2004, 19 pages (Ex. 2033).
10. Amended PCT Patent Application No. PCT/AU98/00648 filed November 11, 1999 (Ex. 2034).

APPENDIX B (STATEMENT OF MATERIAL FACTS)

1. All of the claims of the '512 Application specify that insertions of foreign DNA must be made within certain map unit ranges. (Ex. 2013)

2. Claim 1 of the '512 application (Ex. 2002) is directed to recombinant PAV3 where the insertion site is "selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3." (Ex. 2013).

3. All of the claims in interference specify that an insertion is to be made into at least one of these map-unit ranges (Ex. 2005).

4. A genome is "mapped" by dividing the whole genome into 100 units. (Ex. 2009 Spindler Decl. at ¶ 18).

5. The specific point to which a given map unit (for example, 81) refers depends on the size of the genome. Map unit 81 refers to the 810th base in a genome of 1000 base, and to the 4,050th base in a genome of 5000 bases, for example. (Ex. 2009 Spindler Decl. at ¶ 18).

6. Thus, map units are defined relative to the overall size of the genome. (Ex. 2009 Spindler Decl. at ¶ 37).

7. The precise nucleotides corresponding to map units specified in the claims of the '512 application can only be determined on the basis of the genome size. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 37).

8. The '512 application discloses three different sizes of the PAV3 genome. These are 34.8 kb (page 3, line 28), 35kb (Fig. 1) and 34,094 bp (Fig. 15) (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 37).

9. The '512 application does not indicate which of these three sizes of PAV3 is intended to be the basis of the map units specified in the claims. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 37).

10. The use of map units in the claims of the '512 application does not teach a defined nucleotide region of the genome to a person of ordinary skill in the art. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 37).

11. The correct size of the PAV3 genome is in fact 34,094 bp. (Ex. 2029, Reddy et al., supra entire article, but especially at 414-415; Ex. 2009 Spindler Decl. at ¶ 38).

12. Claim 30 pending in the '512 application is directed to insertions made in the range of map units 81-84. (Ex. 2005; Ex. 2009 Spindler Decl. at ¶ 39).

13. Using the 34.8 kb genome size that Johnson attributed to PAV3 prior to Reddy's publication of the compete PAV3 genome, map units 81-84 would be defined by a scale of 348 nucleotides per map unit. (Ex. 2009 Spindler Decl. at ¶ 39).

14. In a 348 nucleotide per map unit map, map unit 81 corresponds to nucleotide 28,188, and map unit 84 corresponds to nucleotide 29,232. (Ex. 2009 Spindler Decl. at ¶ 39).

15. Based on the correct size of 34,094 bp, disclosed in Fig. 15 of the '512 application, each map unit is 340.94 nucleotides. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 40 (*citing* Ex. 2002)).

16. According to this scale, nucleotide 28,188 would correspond to map unit 82.6 and nucleotide 29,232 would correspond to map unit 85.73. (Ex. 2009 Spindler Decl. at ¶ 40).

17. The nucleotides specified by map units "81-84" when the PAV3 genome is considered to be 34.8 kb are actually the nucleotides corresponding to map units 82.68 to 85.73 when the correct PAV3 size is used. (Ex. 2009 Spindler Decl. at ¶ 40).

18. The shift in the domain of the map unit range is sufficient to partly encompass nucleotides associated with the essential fiber gene. (Ex. 2009 Spindler Decl. at ¶ 40).

19. According to Reddy 1998, the splice acceptor site for the fiber gene of L6 begins at nucleotide 28910. (Ex. 2009 Spindler Decl. at ¶ 40 (*citing* Ex. 2029, Reddy, page 415, Table 2).

20. Each of the map unit ranges specified in the claims of the '512 Johnson application would be similarly affected by the selection of the genome size. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 41).

21. There is a range of results that a person of skill in the art might obtain when interpreting the scope of the claims in light of the different genome lengths recited in the specification. (Ex. 2009 Spindler Decl. at ¶ 42).

22. It is not clear which genome insertions fall within the scope of the claims, and which do not. (Ex. 2009 Spindler Decl. at ¶ 42).

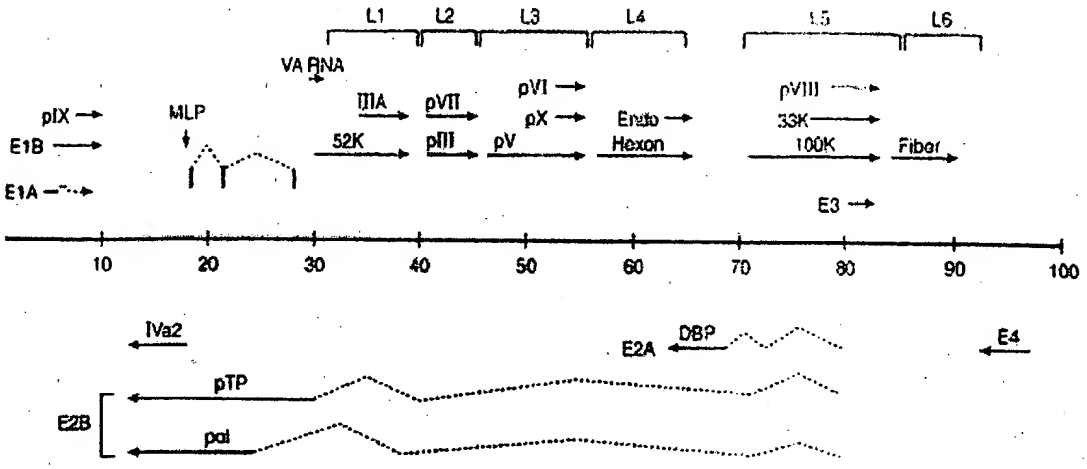
23. The '512 application does not enable or describe producing a replication-defective virus. (Ex. 2002; Ex. 2009 Spindler Decl. at ¶ 59).

24. Johnson's Australian priority application describes the size of the PAV3 genome as being 34.8 kb (Ex. 2003 at page 15, line 11).

25. The reference to 35kb genome size for PAV3 appears for the first time in the original PCT patent application (Ex. 2004, at Figure 1).

26. Johnson added the reference to 34.094 kb genome size for PAV3 when he added Figure 15 to his PCT application through an amendment submitted November 11, 1999, to the International Preliminary Examining Authority ("IPEA") (Ex. 2034; Ex. 2002, Fig. 15).

27. In 1998 Reddy published a "genome map" of PAV3 that lays out the elements of PAV3 on a scale of 100 map units, which is reproduced below. (Ex. 2029, Reddy (1998), at page 416, Figure 1).



The arrows represent genes or groups of genes that are transcribed in PAV3. Above the map unit line are genes that are transcribed left-to-right, and below the line are genes that are transcribed right-to-left.

28. In PAV3, E3 overlaps with the the L5 region which includes the essential gene pVIII. *See* Ex. 2029, Fig. 1; *see also* Exhibit A submitted with Rule 132 declaration of J. Hammond, Feb. 26, 2004, submitted by Johnson during prosecution of the '512 application. (Ex. 2022, Reddy et al., supra at Figures 1 and 2, and page 100; Ex. 2029 Reddy et al., VIROLOGY 251(2):414-426, 420, at Figure 1 reproduced above at paragraph 27 (1998); Ex. 2033; Ex. 2009 Spindler Decl. at ¶ 48)

29. Adenoviruses are DNA viruses that infect the respiratory tract, intestines, and other mucous membranes of a large variety of animals and birds. Known adenoviruses include human ("HAV"), porcine ("PAV"), bovine ("BAV"), mouse ("MAV"), and many others. (Ex. 2014 Thomas Shenk, Ch. 67: Adenoviridae: The Viruses and Their Replication. FIELDS VIROLOGY, 2111-2148 (3rd ed., B.N. Fields et

al. eds. Lippincott – Raven Publishers, Philadelphia (1996); Ex. 2009 Spindler Decl. at 10)

30. Since 1987, researchers have studied the potential use of adenoviruses as vectors for the delivery and expression of foreign DNA. (Ex. 2015 Jean-Luc Imler et al., Trans-Complementation of E1-Deleted Adenovirus: A New Vector To Reduce The Possibility Of Codissemination Of Wild-Type And Recombinant Adenoviruses. HUMAN GENE THERAPY 6, 711-721 (1995); Ex. 2016 Marshall S. Horwitz, Ch. 68: *Adenoviruses,* FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-71, at 2165 (1996); Ex. 2009 Spindler Decl. at ¶ 11)

31. Certain adenoviruses are known to be relatively harmless to the infected immunocompetent human or animal, but highly effective in stimulating an immune response. Scientists realized that a benign adenovirus might be recombined with DNA encoding antigens of more virulent pathogens in order to create a vaccine. (Ex. 2020, T. Tuboly et al., Potential Viral Vectors For The Stimulation Of Mucosal Antibody Responses Against Enteric Viral Antigens In Pigs, research in veterinary science 54, 345-350 (1993); Ex. 2009 Spindler Decl. at ¶ 12)

32. Capsid proteins are critical structural elements that the virus requires to survive. (Ex. 2009 Spindler Decl. at ¶ 14)

33. The proteins that comprise the adenovirus are identified by Roman numerals. Thus, for example, pVIII refers to capsid protein numeral VIII. (Ex. 2009 Spindler Decl. at ¶ 14)

34. The major capsid proteins are also know by other names such "fiber" for pIV, "hexon" for pII, and "penton" for pIII. (Ex. 2014, Shenk et al., supra at 2116, Figure 3; Ex. 2009 Spindler Decl. at ¶ 14)

35. Transcription of adenovirus DNA is accomplished in two phases: the early phase and the late phase. (Ex. 2009 Spindler Decl. at ¶ 15)

36. During the early phase, the virus selectively transcribes certain "early genes" that perform a variety of functions to create the necessary pre-conditions for viral replication. (Ex. 2009 Spindler Decl. at ¶ 15)

37. Early genes are identified by number E1 through E4. (Ex. 2009 Spindler Decl. at ¶ 15)

38. Once early phase transcription is complete, transcription of the "late genes" may begin. (Ex. 2009 Spindler Decl. at ¶ 16)

39. The products of late genes include the capsid proteins. (Ex. 2009 Spindler Decl. at ¶ 16)

40. Viral DNA is transcribed in blocks known as transcription units, which can be processed into multiple mRNAs. (Ex. 2009 Spindler Decl. at ¶ 17)

41. A single mRNA may consist of one or more "open reading frames" each of which can be translated into a protein. (Ex. 2009 Spindler Decl. at ¶ 17)

42. The open reading frame for one gene or protein may overlap with the open reading frame for another. (Ex. 2009 Spindler Decl. at ¶ 17)

43. As a result of overlapping open reading frames in a virus genomic sequence, the same sequence of nucleotides may be part of more than one gene. (Ex. 2009 Spindler Decl. at ¶ 17)

44. In a genome map, each mRNA within each region is represented by an arrow. The body of the arrow represents the nucleotides that are transcribed to produce the mRNA. The direction of the arrow represents the direction of transcription. (Ex. 2009 Spindler Decl. at ¶ 19)

45. The late regions of HAV2 encode structural proteins such as pVIII, which are essential for production of viral particles. (Ex. 2014, Shenk et al., supra at Figures 2B and 3, and 2113-2116, 2118-2120, 2129-2132; Ex. 2009 Spindler Decl. at ¶ 20)

46. The early genes generally encode proteins responsible for replication and transcription of the viral genome, and interactions with the host cell and host immune

response. (Ex. 2014, Shenk et al., supra at Figure 5, and at 2119-2129). (Ex. 2009 Spindler Decl. at ¶ 21)

47. In some circumstances, the products of some early region genes may not be needed for efficient viral growth in cultured cells. (Ex. 2014, Shenk et al., supra at 2134, sentence bridging left and right columns; Ex. 2009 Spindler Decl. at ¶ 21)

48. Scientists have experimented with recombinant techniques to insert foreign DNA into adenoviruses in such a way that the adenovirus retains the ability to replicate because the expression of one or more of the adenovirus's genes may be disrupted depending on where in the genome the foreign genes are inserted. (Ex. 2009 Spindler Decl. at ¶¶ 22, 24)

49. In some cases, the genes that are disrupted may be essential to the formation of the adenovirus rendering the resulting vector "replication-defective.". (Ex. 2009 Spindler Decl. at ¶ 22)

50. In such cases, the adenovirus recombinant cannot form except in the presence of a "helper" cell that is designed to supply the missing protein or proteins that are associated with the disabled gene or genes. (see Ex. 2016, Marshall S. Horwitz, Ch. 68: Adenoviruses, FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-2171, at 2165-2166 (1996); Ex. 2009 Spindler Decl. at ¶ 22).

51. Human adenoviral vectors with insertions in the essential region E1 are produced in complementing cell lines such as the human embryonic kidney "293" cell line, which expresses E1 proteins. (Ex. 2017 F. L. Graham, et al., Characteristics Of A Human Cell Line Transformed By DNA From Human Adenovirus Type 5, JOURNAL OF GENERAL VIROLOGY 36, 59-72 (1977); see Ex. 2016, Horwitz, supra at 2166, right column; Ex. 2009 Spindler Decl. at ¶ 23)

52. The Reddy patent-in-interference (the '343 patent) discloses "helper-dependent" recombinant adenovirus vectors grown in helper cell lines. (Ex. 2001 the '343 patent, col. 22 line 46 – col. 23, line 16)

53. By experimentation it is sometimes possible to identify certain areas of the adenovirus genome that are not essential to viral replication. (Ex. 2009 Spindler Decl. at ¶ 24)

54. When insertions of foreign DNA are made in non-essential regions, the result may be a "helper-independent" recombinant adenovirus. (Ex. 2009 Spindler Decl. at ¶ 24)

55. Adenoviruses have a limit to the amount of DNA that they can encapsidate. (Ex. 2035, Andrew J. Bett et al., Packaging Capacity and Stability of Human Adenovirus Type 5 Vectors JOURNAL OF VIROLOGY 67(10) 5911-5921 (1993)). (Ex. 2009 Spindler Decl. at ¶ 26)

56. In order to make room for foreign genes, it is sometimes useful to delete portions of the native adenovirus DNA. (Ex. 2009 Spindler Decl. at ¶ 26)

57. Deletions of native adenovirus DNA may prevent the expression of any genes that are associated with the deleted nucleotides. (Ex. 2009 Spindler Decl. at ¶ 26)

58. If expression of any essential genes is prevented, then the resulting adenovirus will not assemble into an infectious recombinant adenovirus particle except in a suitable complementary helper cell line. (Ex. 2009 Spindler Decl. at ¶ 26)

59. Johnson claims 26, 31 and 32 in the '512 Application include the additional limitation that the heterologous DNA be inserted into a "non-essential region" of the recombinant porcine adenovirus vector. (Ex. 2005)

60. The art relevant to the technology at issue in this interference is the preparation of animal adenovirus-based vectors for administration to mammals. (Ex. 2009 Spindler Decl. at ¶ 9).

61. A person having ordinary skill in this art in 1996-1999 would have had at least a Master's degree in the biological sciences and/or a Bachelor's degree with at least two years of experience in adenoviruses and have been familiar with scientific and technical publications concerning animal adenoviruses and in particular, porcine adenoviruses. (Ex. 2009 Spindler Decl. at ¶ 9).

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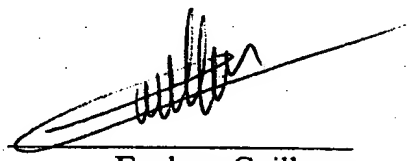
By: 
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